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SYNTHESIS, SPECTROSCOPIC CHARACTERIZATION AND PETRA OSIRIS MOLINSPIRATION (POM) ANALYSES OF DICARBOXYLIC ACID AMIDES

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Key words:

Synthesis, spectrophotometric characterization, Phthalic acid amides, Petra Osiris Molinspiration (POM) analyses

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ABSTRACT: Six new Phthalic acid amides of the general formula C8H5O3-NH-R were prepared by the reaction of Phthalic anhydride with various amines namely Glycine, N, N-diphenyl amine, 1-naphthyl amine, 4-amino toluene-3-sulphonic acid, Toluene-p-sulphonamide, m-nitro aniline. The synthesized compounds were characterized by using IR, 1HNMR & 13CNMR spectroscopy. Petra Osiris Molinspiration (POM) analyses revealed the significant bioactivity by elucidating the structural parameters in drug design of the synthesized compounds. In this work we have performed POM of our synthesized compounds to predict their drug like behaviour. Petra program package was used for the calculation of physiochemical properties of the organic compounds. On the basis of findings of Petra analyses reveals that our synthesized compounds have potential pharmacophores for antiviral and anti bacterial activities. Prediction of bioactivity by Molinspiration software calculates druglikeness score against GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and other enzyme inhibitors (EI). All synthesized compounds showed better activity against ICM, KI, PI and NRL as compared to the reference drug Ciprofloxacin which shows efficient binding to receptors and ion channels. The toxicity risk of synthesized compounds was checked by Orisis software online.

INTRODUCTION: Hippuric acid (N-benzoylglycine) is an α-amido acid containing an acidic COOH, basic NH and a substituent benzoyl group. It is thus capable of forming metal chelates. It has a special biological significance as it is found in the urine of camel.

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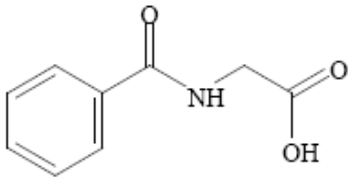
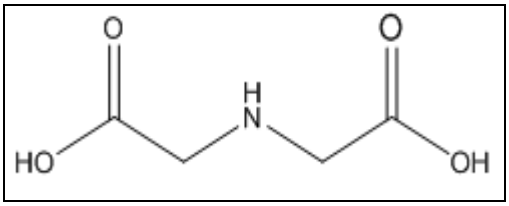
In literature a number of binary and ternary complexes of Hippuric acid and its derivatives have been reported. [1-9]



HIPPURIC ACID

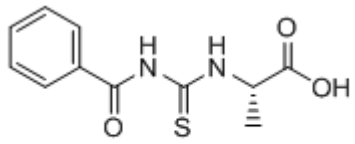
Iminodiacetic acid is a tridentate ligand containing two carboxylate groups and a -NH group. The

structural studies and synthesis, of the coordination complexes of the iminodiacetic acid, its derivatives and mixed ligand complexes have been reported.[10-14] Abdalla and Said [15] have also reported thermal studies on Co (II), Ni (II) and Cu (II) Ternary coordination Complexes of N-(2-acetamido) imino-diacetic acid and imid-azoles.

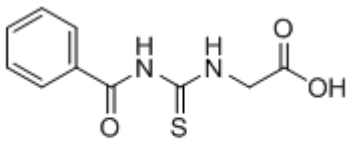


IMINODIACETIC ACID

Complexes of N-[(benzoylamino-thioxomethyl]alanine, N-[(benzoylamino)-thioxomethyl]histidine, and N-[(benzoylamino)-thioxomethyl]cystine with 3d metals and lanthanides are showing great interest as these coordination compounds have shown anti-tumor, anti-viral, bacterio-static and anti-oxidative activity. [16, 17] It is well established that many transition metals [18,19] and rare earth metals [20] amino acids complexes have considerable biological activity, such as antitumor properties. Although transition metal complexes of N-((benzoyl-amino)-thioxo-methyl)glycine [21, 22] and rare earth metals [23] have been prepared.



N-[(benzoylamino)-thioxomethyl]alanine



N-[(benzoylamino)-thioxomethyl]glycine

POM analyses is a modern computational chemistry tool to analyse the bioactivity score and drug likeness of the compounds which helps synthetic chemists to investigate potential for bioactivity of the synthesized compounds or predict the drug like characteristics of compounds which may serve as a smart strategy to save time and resources to reach the desired drug like target molecule without wasting time in trials or unsuccessful attempts to get desired molecular characteristics or bioactivities. POM analyses helps to improve the activity of molecules by predicting their toxicity, lipophilicity and bioactivity and acts as a complementary tool for drug design, hence it has been proved very useful for medicinal chemists.

In this work we have performed POM analyses of synthesized compounds to predict their drug like behaviour. Petra program package was used for the calculation of physiochemical properties of the organic compounds. On the basis of findings of Petra analyses by Hedda et al., it can be concluded that the synthesized compounds have potential pharmacophores for antiviral and anti bacterial activities. Prediction of bioactivity by Molinspiration software calculates druglikeness score against GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and other enzyme inhibitors (EI). The bioactivity score shows that HL-5 has better GPCR score as compared to Ciprofloxacin, showing it as a potential candidate for drug target against GPCR. Similarly synthesized ligands HL-2 and HL-4 have also shown activity against GPCR. To check the toxicity risk of the synthesized compounds we have used Osiris software available online.

Experimental:

Chemicals:

All chemicals used for synthesis were of Analytical grade. Phthalic anhydride, Glycine, N, N-diphenyl amine, 1-naphthyl amine, 4-amino toluene-3-sulphonic acid, Toluene-p-sulphonamide, *m*-nitro aniline were purchased from Aldrich (USA). Ethyl acetate, methanol, and ethanol as well as transition metal salts were purchased from E-Merk (Germany). Synthesis of the ligands HL-1 – HL-6 was carried out by the reported method. [24]

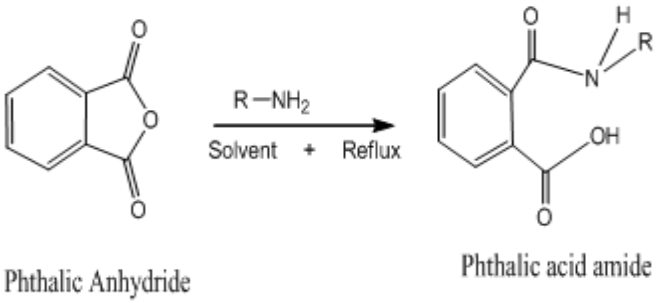
Synthesis:

Synthesis of Phthalic Acid Amides:

Procedure for Synthesis:

10 mmole solution of corresponding amine in 20-30 ml of Ethyl acetate was added with stirring a solution of 1.48g (10mmole) of phthalic anhydride in 20-30 ml of ethyl acetate. After termination of

the reaction (4-5 Hrs), the precipitates were separated by filteration and recrystallized from Ethanol. As shown in the chemical equation.

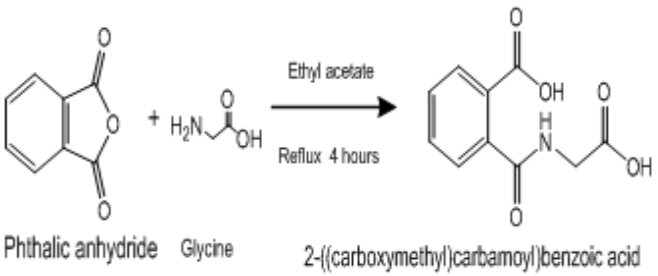


Synthetic Schemes of the Ligands:

Synthesis of Ligand – 1:

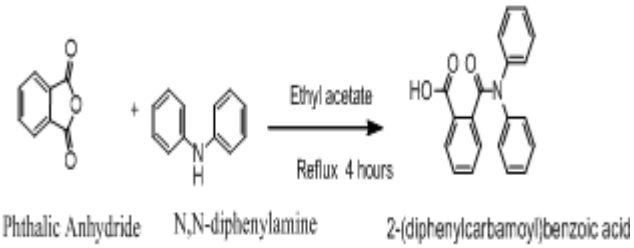
Important IR bands were obtained by using KBr Pellets for Ligand 2-((carboxymethyl) carbamoyl) benzoic acid (**HL-1**) appear at (cm^{-1}): ע $_{asym}$ = 1624, ע $_{sym}$ =1402, ע (NH) = 3180, ע(C=O) = 1676, Aromatic Skeletal Vibration = 1480

The ^{1}H-NMR spectrum of the Ligand in DMSO has given readings at 7.93s ,7.63s, 7.57m, 7.87m, 4H for $–C_6H_4$,8.66s for OC-NH- and 4.32s for $–CH_2$- were detected. The ^{13} C-NMR spectrum of the Ligand in DMSO has shown the signals at 168.9 (1C) for –COOH, 130.08-134.08 (6C) for C_6H_4, 168.92 (1C) O=C-NH-, 40.76 (1C) for $-CH_2$- and 169.57(1C) for -COOH were detected.



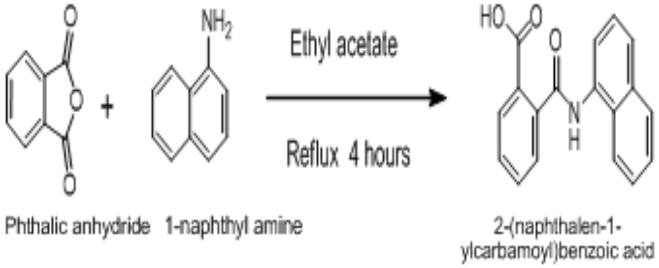
Synthesis of Ligand – 2:

Important IR bands were obtained by using KBr Pellets for Ligand 2-(diphenylcarbamoyl) benzoic acid (**HL-2**) appears at (cm^{-1}): ע $_{asym}$ = 1669, ע $_{sym}$ = 1408, ע (NH) = 3270, ע(C=O) = 1669, Aromatic Skeletal Vibration =1478. The ^{1}H-NMR spectrum of the ligand in D.M.S.O has given readings at 7.57-8.15 (m) 4H for C_6H_4-, 6.83-7.25 (t) 10 H $–(C_6H_5-)_2$, 13.16(s) 1H , for –COOH are detected. The ^{13}C-NMR spectrum of the ligand D.M.S.O has given readings at 169.17 (1C) –COOH, 128.81-133.27 (6C) C_6H_4-, 169.17 (1C) O=C-NH, 143.84,117.31,128.81,120.09,128.81,117.31 (12C) $(C_6H_5-)_2$ have been detected.

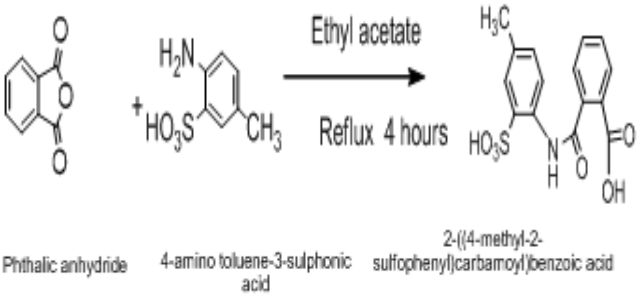


Synthesis of Ligand – 3:

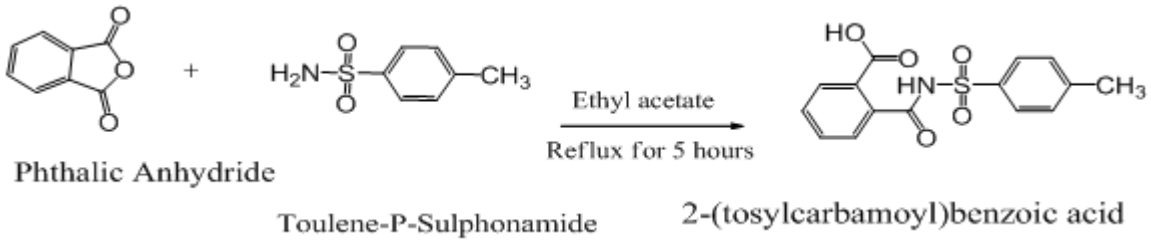
Important IR bands were obtained by using KBr Pellets for ligand 2-(naphthalen-1-ylcarbamoyl) benzoic acid (**HL-3**) appear at (cm^{-1}): ע $_{asym}$ = 1657, ע $_{sym}$ = 1365, ע (NH) = 3279, ע(C=O) = 1644, Aromatic Skeletal Vibration = 1403. The ^{1}H-NMR spectrum of the ligand in D.M.S.O has given readings at 7.84, 7.92 (d), 8.21,8.24(t) 4H, for C_6H_4- , 8.05(d) 1H for –NH- , 7.56-7.74(m) 7H for $C_{10}H_7$-. and 10.40(s) 1H for, –COOH have been detected. The ^{13}C-NMR spectrum of the ligand in D.M.S.O gave readings at 169.16(1C), for COOH, 128.89,128.27,127.17,134.62,133.32,131.24 (6C), for C_6H_4 169.16 (1C) O=C-NH- , 144.8, 134.6,108.10,126.19,116.05,128.27,125.96, 124.14, 123.22 , 122.77 (10C) for , $-C_{10}H_7$ have been detected.



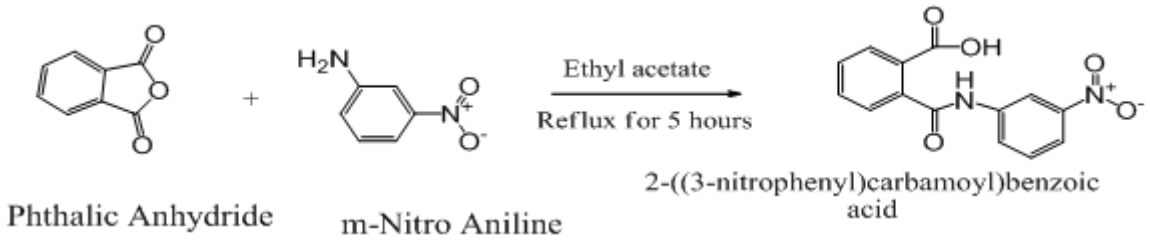
Synthesis of Ligand – 4:



Synthesis of Ligand – 5:



Synthesis of Ligand – 6:



RESULT AND DISCUSSION:

Synthesis of Ligands (HLs):

Six new Phthalic acid amides (HL1-HL6) of the general formula $C_8H_5O_3$-NH-R were synthesized by the method reported in the literature [24-26] as shown in the scheme 1 with all necessary conditions. In particular, the amides have shown antiflammatory, hemoststic, and anticoagulant [27, 28] and antatherosclerotic [29] properties. The synthesized ligands acids (HL) were crystalline solids having high melting points. These ligands have been characterized by Infrared (IR), H^1-NMR and C^{13}-NMR Spectroscopy.

Where **R** =

HL-1= - CH_2COOH

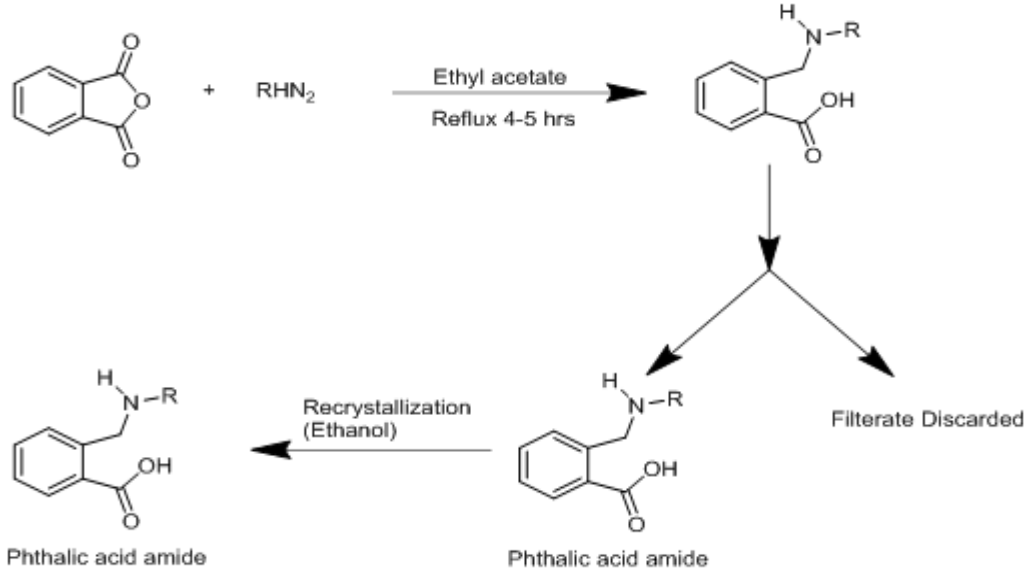
HL-2 = - $(C_6H_5)_2$

HL-3 = - $C_{10}H_7$

HL-4= - $C_8H_5O_3$

HL-5= - $C_7H_7SO_2$

HL-6= - $C_6H_4NO_2$



SCHEME 1: SYNTHESIS OF PHTHALIC ACID AMIDES (HL1-HL6)

Spectroscopic Characterization of Compounds:

Infrared (IR) Spectra of the Ligands:

Infrared Spectra of the synthesized ligand acids (HL1-HL3) have been obtained on KBr pellets in the range of 4000-700 cm^{-1}. The Ligands (HL1- Hl-3) have shown $ע_{asym}$(COO) values at 1624, 1669 and 1657cm^{-1} , while their $ע_{sym}$(COO) values were recorded at 1402, 1408 and 1365 cm^{-1} respectively as mentioned in **Table 1** The ligands have also shown the peaks of ע (NH) at 3180, 3270 and 3279 cm^{-1}, and of ע(C=O) at 1676, 1669 and 1644 cm^{-1} respectively as shown in **Fig.1** to **Fig 3**.

TABLE 1: INFRARED ABSORPTION FREQUENCIES (CM^{-1}) OF LIGANDS

Compound	ע (COO)			ע (NH)	ע(C=O)	Aromatic Skeletal Vibration
	$ע_{asym}$	$ע_{sym}$	Δע			
HL-1	1624	1402	222	3180	1676	1480
HL-2	1669	1408	261	3270	1669	1478
HL-3	1657	1365	292	3279	1644	1403

^{1}H-NMR Spectra of the Ligands (HLs):

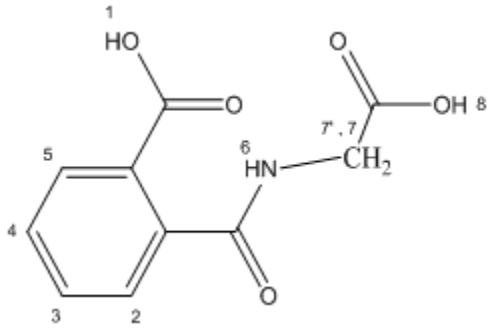
HL-1 2-[(carboxymethyl)carbamoyl] benzoic acid:

The ^{1}H-NMR spectrum of the ligand 2-((carboxymethyl)carbamoyl) benzoic acid (**HL-1**) in DMSO signals at 7.93s ,7.63s, 7.57m, 7.87m, 4H for $–C_6H_4$,8.66s for OC-NH- and 4.32s for $–CH_2$- have been recorded , as shown in the **Table 2** & **Fig.4.**

TABLE 2: ^{1}H-NMR OF THE LIGAND HL-1

H atom no.	H1	H2	H3	H4	H5	H6	H7	H7'	H8
Chemical Shift	----	7.93	7.63	7.57	7.87	8.66	4.32	4.32	-----
Multiplicity	----	s	s	m	m	s	s	s	-----

According to the ^{1}H-NMR structure of the ligand with numbered H-atom is shown as;



2-((carboxymethyl)carbamoyl) benzoic acid

HL-2: 2-(diphenylcarbamoyl) benzoic acid:

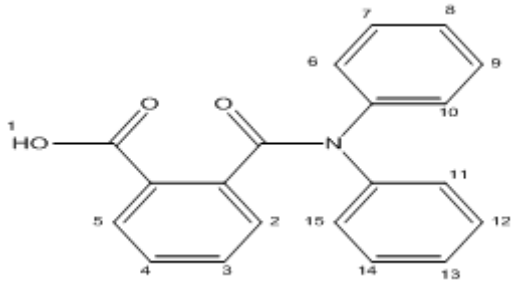
The ^{1}H-NMR spectrum of the ligand 2-(diphenylcarbamoyl) benzoic acid (**HL-2**) in DMSO signals at 7.57-8.15 (m) 4H for C_6H_4-, 6.83-7.25 (t) 10 H $–(C_6H_5-)_2$, 13.16(s) 1H , for –COOH have been recorded, as shown in **Fig.5** & **Table 3** in detail.

TABLE 3: ^{1}H-NMR OF THE LIGAND HL-2

H atom No.	Chemical Shift	Multiplicity
H1	13.16	s
H2	7.69	m
H3	7.66	m
H4	7.57	m
H5	8.15	m
H6	7.25	t
H7	7.05	t

H8’	6.83	t
H9	7.20	t
H10	7.22	t
H11	7.25	t
H12	7.05	t
H13	6.83	t
H14	7.20	t
H15	7.22	t

By using the above described data the possible chemical structure of the ligand acid can be expressed with numbered H-atoms, as;



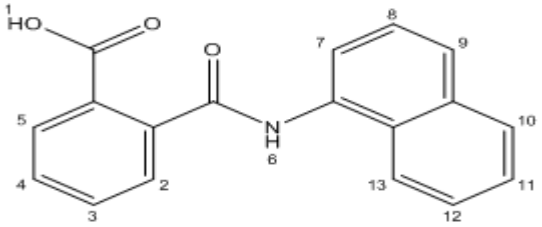
HL- 3. 2-(naphthalen-1-ylcarbamoyl) benzoic acid:

The ^{1}H-NMR spectrum of the ligand 2-(naphthalen-1-ylcarbamoyl) benzoic acid (**HL-3**) in DMSO signals at 7.84, 7.92 (d), 8.21,8.24(t) 4H, for C_6H_4- , 8.05(d) 1H for –NH- , 7.56-7.74(m) 7H for $C_{10}H_7$-. and 10.40(s) 1H for, –COOH have been recorded, as shown in **Fig 6** and **Table 4** in detail;

TABLE 4: ^{1}H-NMR OF THE LIGAND HL-3

H atom No.	Chemical Shift	Multiplicity
H1	10.40	s
H2	8.21	t
H3	7.92	d *J* = 7.5
H4	7.84	d *J* = 8.1
H5	8.24	t
H6	8.05	d *J* = 7.8
H7	7.56	m
H8’	7.58	m
H9	7.61	m
H10	7.67	m
H11	7.69	m
H12	7.71	m
H13	7.74	m

By using the above described data the possible chemical structure of the ligand acid can be expressed with numbered H-atoms, as;



^{13}C-NMR Spectra of the Ligands (HLs):

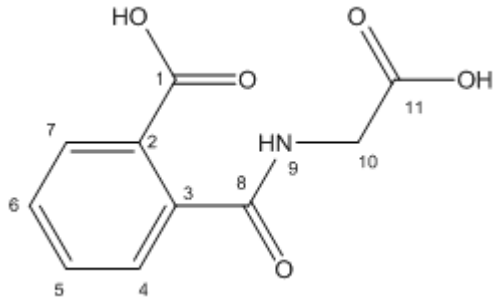
HL-1 2-((carboxymethyl)carbamoyl) benzoic acid:

The ^{13}C-NMR spectrum of the ligand 2-((carboxymethyl)carbamoyl) benzoic acid **(HL-1)** in DMSO have shown the signals at 168.9 (1C) for –COOH, 130.08-134.08 (6C) for -C_6H_4, 168.92 (1C) O=C-NH-, 40.76 (1C) for -CH_2- and 169.57(1C) for -COOH have been recorded **Fig.7**, as shown in detail in the **Table 5.**

TABLE 5: ^{13}C-NMR OF THE LIGAND HL-1

C No.	Chemical Shift
C1	168.92
C2	130.08
C3	130.08
C4	131.06
C5	134,08
C6	103.08
C7	131.06
C8	168.92
N9	---------
C10	40.76
C11	169.57

By using the above described data the possible chemical structure of the ligand acid can be expressed with numbered C-atoms, as;



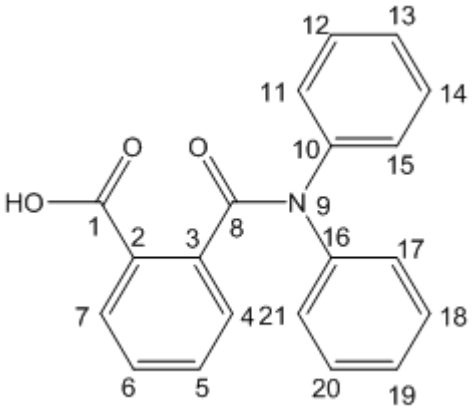
HL-2 2-(diphenylcarbamoyl) benzoic acid:

The ^{13}C-NMR spectrum of the ligand 2-(diphenylcarbamoyl) benzoic acid (**HL-2**) in D.M.S.O have shown the peaks at 169.17 (1C) –COOH, 128.81-133.27 (6C) C_6H_4-, 169.17 (1C) O=C-NH- , 143.84, 117.31, 128.81, 120.09, 128.81, 117.31 (12C) (C_6H_5-)$_2$ **Fig.8** , as shown in detail in the **Table 6**

TABLE 6: ^{13}C-NMR OF THE LIGAND HL-2

Carbon Atom No.	Chemical Shift
C 1	169.17
C 2	131.25
C 3	129.6
C 4	128.81
C 5	133.27
C 6	133.27
C 7	131.25
C 8	169.17
N 9	--------
C 10	143.84
C 11	117.31
C 12	128.81
C 13	120.09
C 14	128.81
C 15	117.31
C 16	143.84
C 17	117.31
C 18	128.81
C 19	120.09
C 20	128.81
C 21	117.13

By using the above described data the possible chemical structure of the ligand acid can be expressed with numbered C-atoms, as



2-(diphenylcarbamoyl) benzoic acid

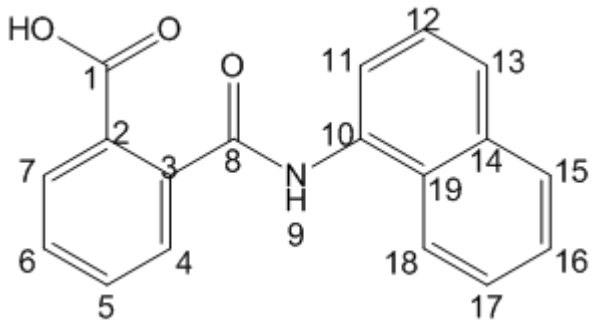
HL-3 2-(naphthalen-1-ylcarbamoyl) benzoic acid:

The ^{13}C-NMR spectrum of the ligand 2-(naphthalen-1-ylcarbamoyl) benzoic acid (**HL-3**) in D.M.S.O have shown the peaks at 169.16(1C), for COOH, 128.89, 128.27, 127.17, 134.62, 133.32, 131.24 (6C), for C_6H_4 169.16 (1C) O=C-NH-, 144.8, 134.6, 108.10, 126.19, 116.05, 128.27, 125.96, 124.14, 123.22 , 122.77 (10C) for , -$C_{10}H_7$, as shown in the **Fig 8** & **Table7**.

TABLE 7: ^{13}C-NMR OF THE LIGAND HL-3

Carbon Atom No.	Chemical Shift
C 1	169.16
C 2	128.89
C 3	128.27
C 4	127.17
C 5	134.62
C 6	133.32
C 7	131.24
C 8	169.16
N 9	-------
C 10	144.8
C 11	134.6
C 12	108.10
C 13	126.19
C 14	116.05
C 15	128.27
C 16	125.96
C 17	124.14
C 18	123.22
C 19	122.77

By using the above described data the possible chemical structure of the ligand acid can be expressed with numbered C-atoms, as;



2-(naphthalen-1-ylcarbamoyl) benzoic acid

4. POM Analyses of the synthesised compounds:

POM analyses is a modern computational chemistry tool to analyse the bioactivity score and drug likeness of the compounds which helps synthetic chemists to investigate potential for bioactivity of the synthesized compounds or predict the drug like characteristics of compounds which may serve as a smart strategy to save time and resources to reach the desired drug like target molecule without wasting time in trials or unsuccessful attempts and to get desired molecular characteristics or bioactivities. POM analyses helps to improve the activity of molecules by predicting its toxicity, lipophilicity and bioactivity and acts as a complementary tool for drug design hence it has been proved very useful for medicinal chemist.

In this work we have performed POM of our synthesized compounds to predict their drug like behaviour. Petra program package was used for the calculation of physiochemical properties of the organic compounds. On the basis of findings of Petra analyses by Hedda et al., we can conclude that our ligands have potential pharmacophores for antiviral and anti bacterial activities. The logP value estimates the logarithm of octanol/water partition coefficient of organic chemicals and drugs which uses an atom/fragment contribution method. LogP is the measure of hydrophilicty of the compounds.

High logP values or low hydrophilicites cause poor intestinal absorption or membrane permeation. So for good absorption their logP values must not exceed 5.0. All our synthesized compounds have values less than five so they have good membrane permeability. TPSA (Total Polar Surface Area) is the sum of surfaces of all the polar atoms present in

the molecule like oxygen, nitrogen, and attached hydrogen with polar bonds. TPSA predicts the drug transport properties through the intestines and blood brain barriers. Both TPSA and Volume of molecule are important parameters to predict the transport properties as they are inversely proportional to the percentage absorption (%ABS) it means that low values of TPSA and smaller volume molecules are easy to cross the membranes. The %ABS can be calculated by using TPSA values putting in equation,

$$\%\ ABS = 109 \pm 0.345 \times TPSA.$$

The calculated %ABS values show that HL-4 and HL-6 show moderate absorption while HL-2 and HL-3 show better absorption as compared to reference drug. The number of rotatable bonds (nrotb) and Lipinski rule of five which gives an insight to membrane permeability is used as a filter for drug like properties. It is suggested that passing oral bioavailibity criteria the number of rotatable bonds should be ≤ 10. All our synthesized compounds have passed these criteria as well as their values of number of rotatable bonds lie between 3 and 4 also showing their conformational flexibility.

According to the rule for good membrane permeability the values should be, log P ≤ 5, molecular weight ≤500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤5. None of the compounds violated Lipinski criteria. Aqueous solubility of a compound is very important for its absorption and distribution in cells. A low solubility shows poor absorption. LogS value shows log base 10 of the solubility measured in mol/liters. Most of the drugs in market have logS values greater than -4 and less than 0. All our compounds except HL-2 and HL-3 showed log S values between 0 and -4 while HL-5 has greatest value i.e 2.98.

Prediction of bioactivity by Molinspiration software calculates drug likeness score against GPCR ligands, ion channel modulators (ICM), kinase inhibitors (KI), nuclear receptor ligands (NRL), protease inhibitors (PI) and other enzyme inhibitors (EI). Bioactivity score shows that HL-5 has better GPCR score as compared to Ciprofloxacilin showing it as a potential candidate for drug target against GPCR. HL-2 and HL-4 also show activity against GPCR. All synthesized compounds showed better activity against ICM, KI, PI and NRL as compared to the reference drug Ciprofloxacin which shows efficient binding to receptors and ion channels. The EI values showed good EI activity but not greater than Ciprofloxacin (Cip), HL-2 and HL-6 showed least activity as EI as compared to other synthesized ligands and reference drug Ciprofloxacin as shown in **Table 8**.

To check the toxicity risk of our synthesized compounds we have used Osiris software available online. Osiris calculations reveal that HL-1, HL-2, and HL-5 are completely non toxic as per their effect as mutagenic, tumorigenic, irritant and reproductive effective and have less toxicity than reference drug Ciprofloxacin. While HL-3, HL-4 and HL-6 showed some toxicity according to the **Table 9** HL-1, HL-2, and HL-5 are showing good drug score according to the POM analyses.

TABLE 8: MOLINSPIRATION PROPERTY AND MOLINSPIRATION BIOACTIVITY SCORE DATA OF THE SYNTHESIZED COMPOUNDS

data	HL-1	HL-2	HL-3	HL-4	HL-5	HL-6	Cip
miLogP	-0.01	4.29	3.51	-0.28	2.01	2.29	-0.70
TPSA	103.7	57.61	66.40	120.77	100.54	112.22	74.57
%ABS	73.46	89.12	86.09	67.6	74.31	70.28	83.27
natoms	16	24	22	23	22	21	24
MW	223.18	317.34	291.31	335.34	319.34	286.24	331
nON	6	4	4	7	6	7	6
nOHNH	3	1	2	3	2	2	2
nviolations	0	0	0	0	0	0	0
nrotb	4	4	3	4	4	4	3
volume	186.23	285.63	257.83	269.85	261.83	237.17	285.46
GPCR L	-0.21	0.07	0.00	0.04	0.14	-0.28	0.12
ICM	-0.10	-0.17	-0.06	-0.14	-0.30	-0.27	-0.04
KI	-0.54	-0.10	0.05	-0.27	-0.11	-0.23	-0.07

PI	-0.15	-0.12	-0.05	0.10	0.17	-0.30	-0.21
NRL	-0.26	-0.01	-0.04	-0.44	0.05	-0.28	-0.19
EI	0.05	-0.07	0.03	0.11	0.13	-0.17	0.28

TABLE 9: OSIRIS CALCULATIONS OF DATA OF THE SYNTHESIZED COMPOUNDS

Compounds	Toxicity Risks[a]				Bioavailability and Drug-Score[b]					
	MUT	TUM	IRRIT	RE	cLogP	Solubitiy	MW	TPSA	Druglikness	Drug Score
HL-1	-	-	-	-	-0.29	-1.41	223	103.7	-7.39	0.48
HL-2	-	-	-	-	3.2	-5.14	317	57.61	-4.8	0.33
HL-3	+	+	-	-	3.49	-4.75	291	66.4	-3.35	0.13
HL-4	+	-	+	-	0.41	-2.09	335	129.1	-4.91	0.17
HL-5	-	-	-	-	2.11	2.98	319	108.9	-8.21	0.44
HL-6	-	-	-	+	1.69	-3.78	288	110.1	-3.22	0.26
Cip	-	-	-	+[a]	1.63	-3.42	331.34	74.57	2.33	0.65

(-): Not toxic; (+a): slightly toxic; **(+)**: highly toxic. A) mut: mutagenic; tum: tumorigenic; irrit: irritant; re: reproductive effective. B) bioavailability and drug score.

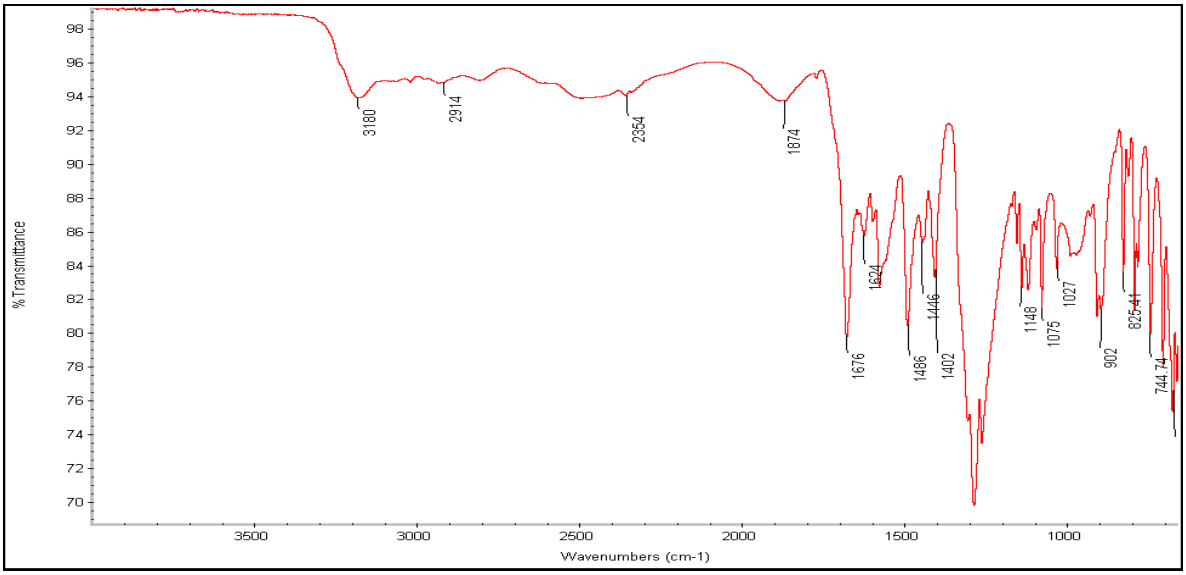


FIG 1: IR SPECTRUM OF HL-1

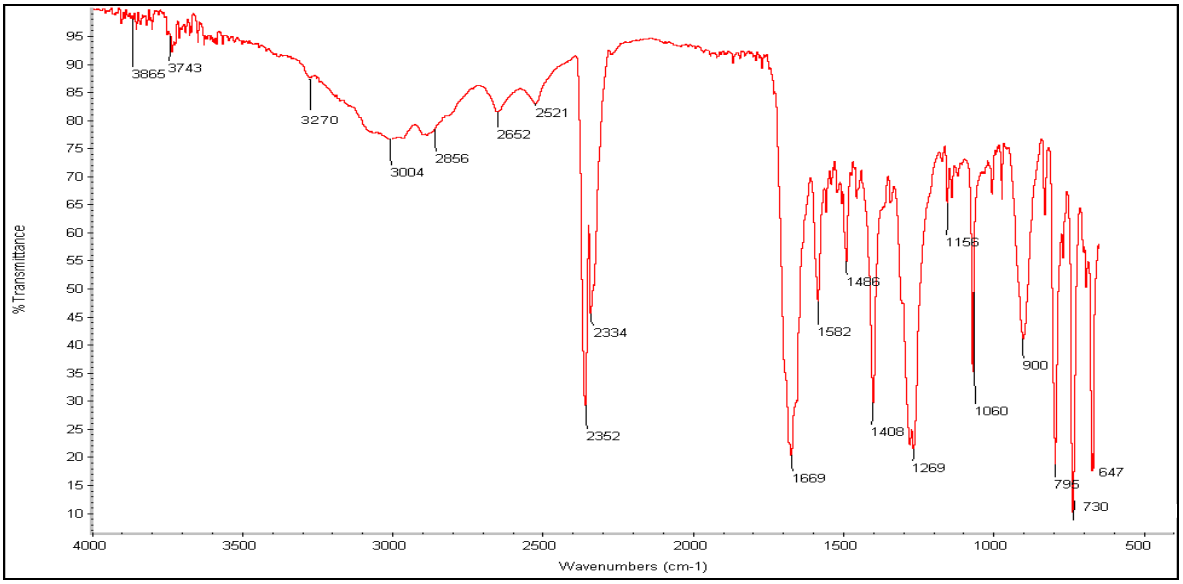


FIG 2: IR SPECTRUM OF HL-2

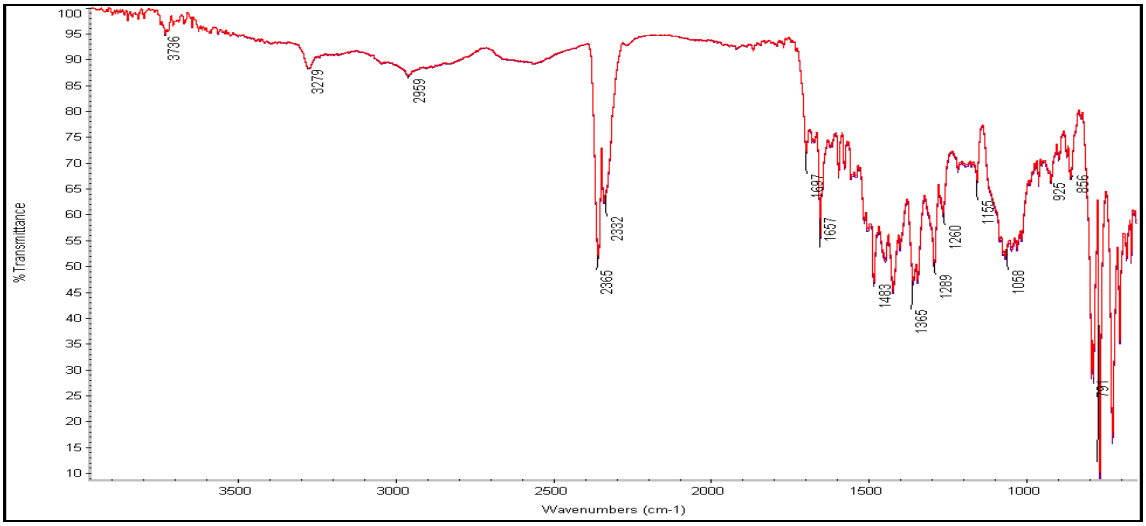


FIG. 3: IR SPECTRUM OF HL-3

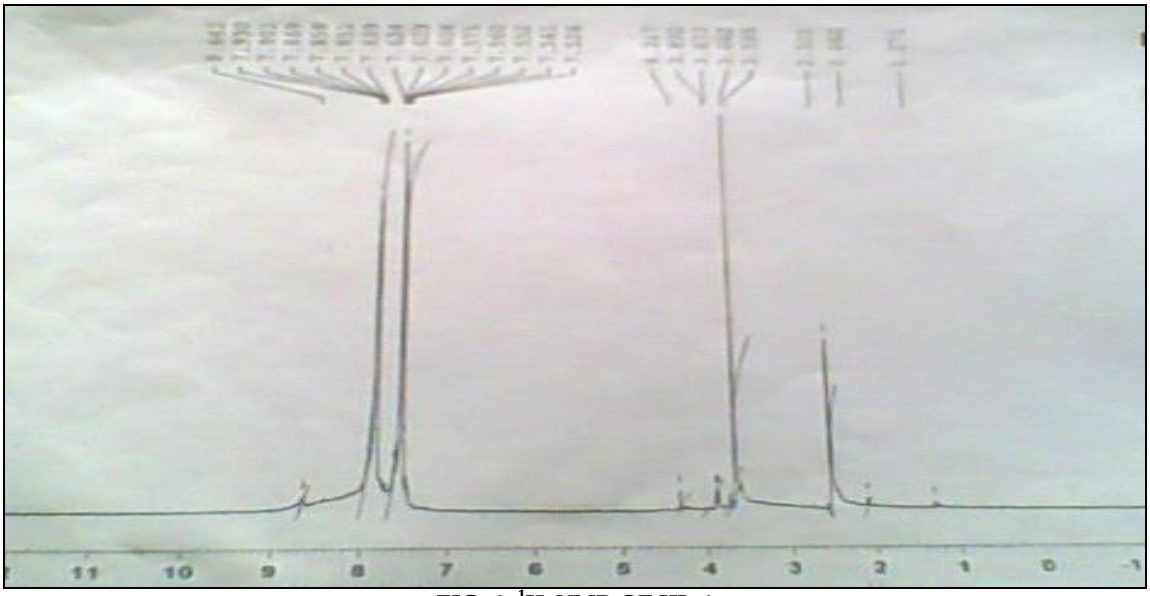


FIG. 4: ^{1}H_NMR OF HL-1

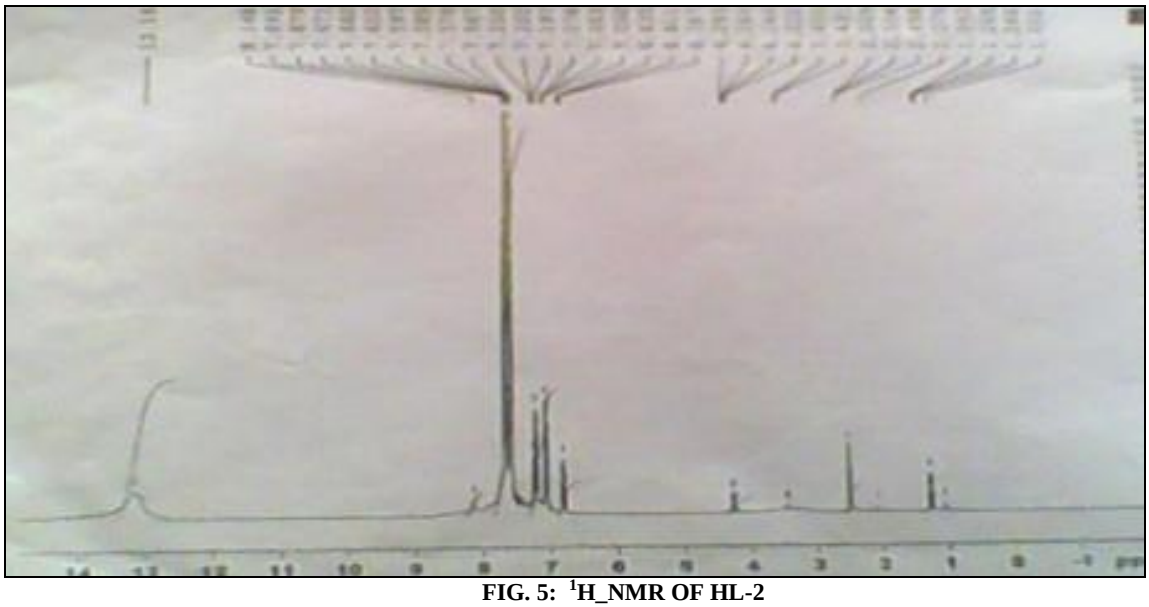


FIG. 5: ^{1}H_NMR OF HL-2

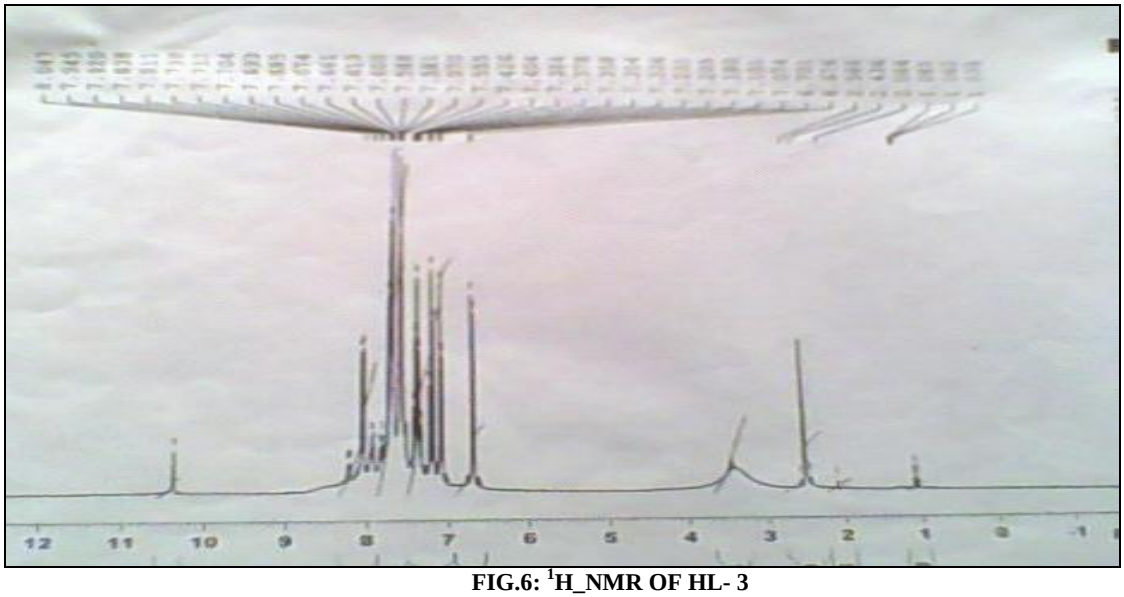


FIG.6: ^{1}H_NMR OF HL- 3

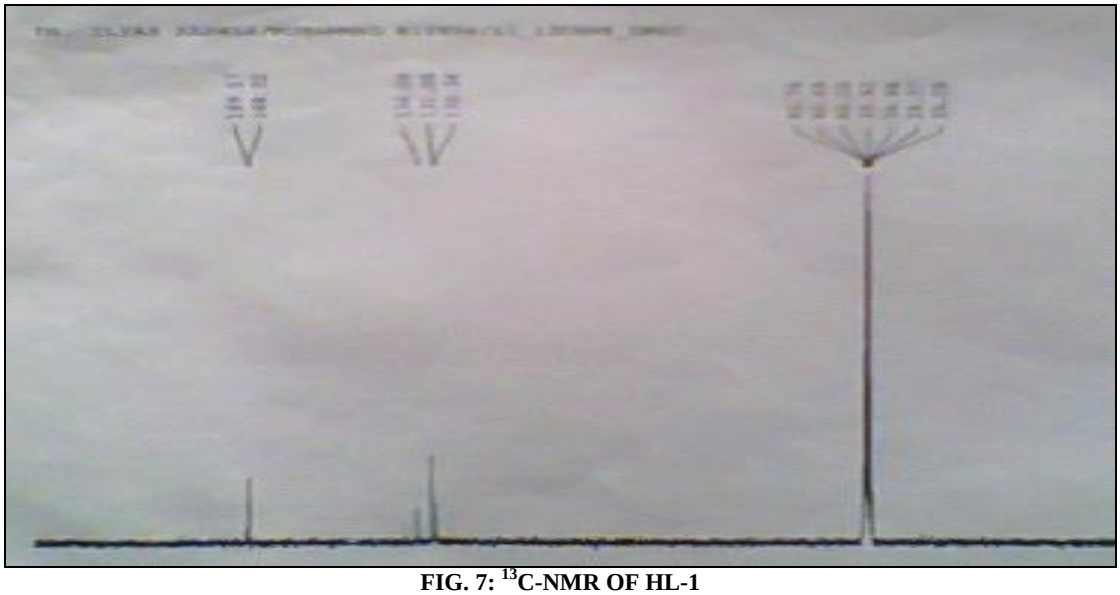


FIG. 7: ^{13}C-NMR OF HL-1

FIG. 8: 13C_NMR OF HL-2

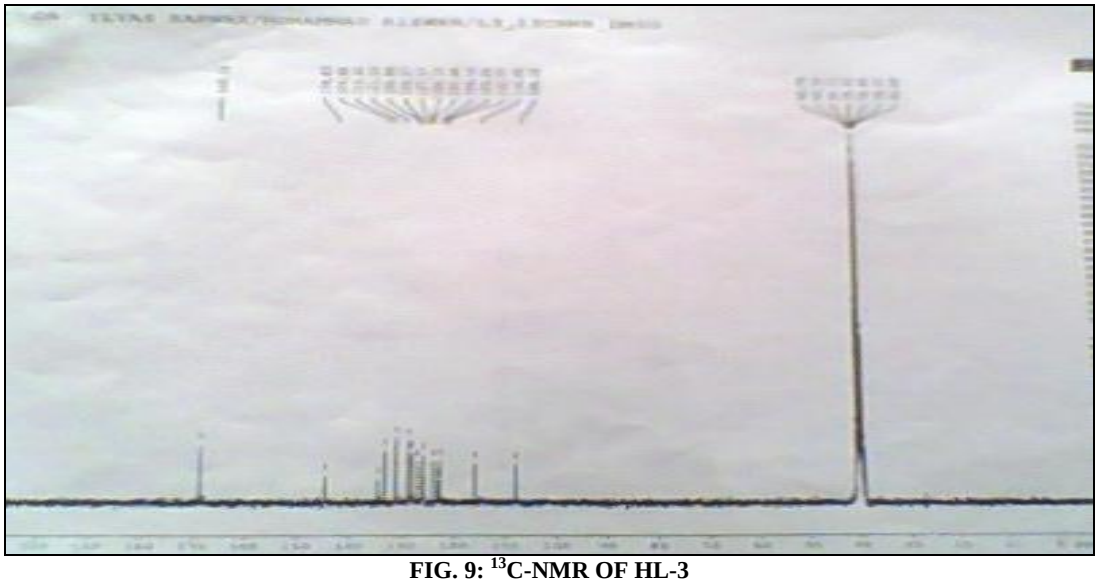


FIG. 9: ^{13}C-NMR OF HL-3

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